REMARKS

I. Claims in the Case

No claims have been canceled or added. Claim 10 has been amended. Claims 1-20 and 22-49 are currently pending and under examination.

III. Provisional Double Patenting

The Action first provisionally rejects claims 10-20, 25 and 39-49 on the basis of double patenting over copending application USSN 08/726,811. Applicants believe that the reference to copending application USSN 08/726,811 is a typographical error since the previous action, dated August 28, 2001, refers to copending application USSN 08/726,211. Therefore, Applicants response is in reference to the '211 application.

Additionally, Applicants note that the issue fee has been paid in the '211 case, but it has yet to issue. However, Applicants have, for the Examiner's convenience, enclosed a copy of the allowed claims that will issue. The basis of the double patenting rejection is not entirely clear, as Applicants are unaware of any claims present in the '211 case that are identical to any claims pending in the present case (it being noted that the rejection is a straight double patenting rejection).

Furthermore, the Action fails to identify the claims from the '211 case that are relied upon to form the basis of the double patenting rejection, and for this reason alone the rejection is inadequate and inappropriate.

IV. Corrected Filing Receipt

Applicants note that a request for corrected filing receipt was filed with the PTO in the case on April 24, 2000, and yet this request has never been acted upon. The Examiner is

requested to act upon this request. If the request has been lost, the Examiner is requested to contact the undersigned representative.

V. Rejection of Claims as Obvious

The Action next rejects claims 1-9, 21-24 and 26-38 as obvious over the combination of Evan or Reed or Green *et al.*, each in view of Lopez-Berestein *et al.*, US 5,855,911.

In response, Applicants note that Lopez-Berestein *et al.* is not available as prior art under 35 U.S.C. §102(e)/103(a) in that there is a common obligation of assignment. The present case is a nationalization of PCT US/97/18348 filed 10/3/97 and a continuation of USSN 08/726,211, filed October 4, 1996. The present case is assigned to the same assignee as the '911 patent, Board of Regents of The University of Texas System, and the undersigned Applicants' representative hereby verifies that the present inventors were obligated to assign their rights in the invention of the '911 patent to the Board of Regents of the University of Texas System at the time the present invention was made, which was also assigned to the same assignee. Thus, it is submitted that the '911 patent is not available as prior art.

VI. Rejection of Claims as Lacking Enablement

Lastly, the Action rejects claims 10-20, 25 and 39-49 as lacking enablement for reasons as previously stated.

In response, Applicants incorporate by reference all previous arguments, and will rely on such arguments and evidence before the Board. The claims have been amended to refer to Bcl-2 associated "cancers" to address the Bcl-2 associated "disease" issue.

Applicants will respond briefly to the two or three new matters raised by the Examiner, which are submitted to be irrelevant to the enablement issues for the reasons stated below:

- Beginning at the bottom of page 7 of the Action, Crooke is cited for the proposition that on cannot predict *in vivo* pharmacokinetics of antisense compounds based on *in vitro* studies. In response, it is first noted that this section simply deals with pharmacokinetics of a compound, not on efficacy, etc. Applicants are not aware of any rule that a compound's pharmacokinetics must be ascertained and disclosed, particularly in light of the fact that neither Applicants' claims nor the animal/cell based studies relied upon to prove enablement, do not make reference to any particular pharmacokinetics and are not directed to looking at uptake (which was a problem with some of the early antisense structures). Thus, even if it is true that one cannot predict "pharmacokinetics" of a compound based on in vitro studies, this is irrelevant to the question at hand, whether Applicants' specification and evidence demonstrates utility of the claimed antisense in treating Bcl-2 associated cancers.

- The Action next makes reference to an excerpt apparently dealing with the nude mouse model. Unfortunately, the Action fails to identify where in the article this excerpt appears, and the Applicant's are unable to find it. However, from the little bit cited by the Examiner, we are unable to identify what the Examiner is relying upon in the context of this rejection. Indeed, the first excerpt appears to actually support a conclusion of enablement, not *vice versa*. In any event, the Examiner has failed to cite any passage that gives rise to any inference of non-enablement of the present invention. Applicant's also refer again to the numerous references submitted in response to the Office Action dated July 10, 2000 that demonstrate the usefulness of the nude mouse model system in predicting efficacy of disease treatment.

- The Examiner lastly refers to Crooke as calling for an identification of the mechanism of a particular antisense. This consideration is, of course, irrelevant here as the mechanism of the

Bcl-2 gene as an anti-apoptotic protein is well established. Furthermore, while the identification of a mechanism may be of interest scientifically, it is hardly an issue relevant to enablement.

It is noted that the Examiner has in no way addressed the matters raised in the subject declarations of record which demonstrate a reasonable conclusion of enablement, and that the "evidence" presented from the Crooke article are simply not directed to the enablement issues and thus should be disregarded.

- Applicants present herewith additional evidence of enablement with respect to the state of art of clinical trials being conducted by Genta Incorporated, New Jersey, U.S.A., using a Bcl-2 antisense oligonucleotide referred to as Genasense™, which are also described in **Appendix A** and **Appendix B** submitted herewith. This evidence was not presented earlier in the case as Applicants believe that the specification provides sufficient enablement for the claims in itself. However, the Examiner has persisted with the enablement rejections based on the "unpredictability of the art," despite Applicant's previous arguments. Applicants contend that the present evidence removes any doubt about the predictability of gene therapy with regard to antisense molecules, and in particular with regard to Bcl-2 antisense therapies. Therefore, entry and consideration of the present evidence is respectfully requested.

Genasense™ is a phosphorothioate antisense oligonucleotide complementary to the first six codons of the initiating sequence of the human *bcl-2* mRNA and inhibits the production of Bcl-2. As set forth in **Appendix A**, Genasense™ is:

> ....**currently in late-stage clinical trials** for treatment of melanoma, multiple myeloma and chronic lymphocytic leukemia. The current studies with Genasense™ target acute myeloid leukemia and cancers of the prostate, lung, colon, and breast. Genasense™ is being used to enhance the activity of other standard types of anticancer therapy. **The drug has received both "Fast Track" and "Orphan Drug" designation from the U.S. Food and Drug Administration. (emphasis added)**

Appendix A also recites that "**Genasense™ has been administered to more than 500 patients worldwide since 1995.**" **Appendix A** also contains several press releases regarding clinical trials of Genasense™.

Applicants also present a copy of a publication by Chi *et al.*, (*Clin. Cancer Res.* Dec;7(12):3920-7, 2001), submitted herewith as **Appendix B,** which describes a **phase I clinical trial** of Genasense™ in patients with metastatic hormone-refractory prostate cancer. Chi *et al.*, show that two patients out of five had >50% reduction of the prostrate-specific antigen and peripheral blood Bcl-2 protein expression decreased in all the five patients treated with Genasense™. Furthermore, biologically active doses of Genasense™ showed a good tolerability in a combination therapy with the cytotoxic agent, mitoxantrone, with no dose-limiting toxicities. Applicants submit that the studies described in **Appendix A** and **Appendix B** demonstrate the success of delivery, uptake and targeting as well as the safety of gene therapeutic methods that use antisense oligonucleotides and especially of antisense oligonucleotides specific to Bcl-2.

Applicants would also like to cite the MPEP §2107.03 on the U.S. Food and Drug Administration (FDA), approval and clinical trials. With respect to Genasense™, the FDA has allowed the drug to be used in clinical trials. As stated in MPEP §2107.03:

> ....before a drug can enter human clinical trials, the sponsor, must provide a convincing rationale to those especially skilled in the art (*e.g.*, the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary.

As set forth in the discussion above, both **Appendix A** and **Appendix B** describe human clinical trials using a Bcl-2 antisense oligonucleotide as a therapeutic product. The establishment of clinical trials of such a therapeutic product is reasonably predictive of the success of methods

that utilize antisense oligonucleotides, especially antisense molecules that target the same gene (Bcl-2).

Experts at the FDA, who are experts designated by Congress, have assessed Genasense™, an antisense drug that also targets Bcl-2, and the corresponding therapeutic methods and found them satisfactory enough to allow clinical trials on human patients, the Examiners allegation that the methods of the present invention are not enabled due to the "unpredictability of the art", *i.e.*, the field of gene therapy is unsound and is in fact contrary to this evidence. Thus, Applicants request withdrawal of the enablement rejections.

VII. Conclusion

It is believed that the present claims are in condition for allowance. It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/UTSC:550US.

Respectfully submitted,

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